

Is the Decline of the Increasing Incidence of Non-Hodgkin Lymphoma in Sweden and Other Countries a Result of Cancer Preventive Measures?

Lennart Hardell^{1,2} and Mikael Eriksson³

¹Department of Oncology, University Hospital, and ²Department of Natural Sciences, Örebro University, Örebro, Sweden; ³Department of Oncology, University Hospital, Lund, Sweden

Is the decline of the increasing incidence of non-Hodgkin lymphoma (NHL) in Sweden and other countries a result of cancer preventive measures? The yearly age-standardized incidence of NHL increased significantly in Sweden during 1971–1990, for men an average of 3.2% and for women 3.1%. The corresponding figures for 1991–2000 were –0.8% and –0.2%, respectively. A decline of the increasing incidence has also been seen in other countries, such as the United States, Finland, and Denmark. Immunosuppression is one established risk factor for NHL, possibly with interaction with Epstein-Barr virus. Phenoxyacetic acids and chlorophenols, both pesticides, have been associated with NHL. Use of these chemicals was banned in Sweden in 1977 and 1978, respectively. Also, persistent organic pollutants such as polychlorinated biphenyls, hexachlorobenzene, chlordanes, and dioxins have been shown to increase the risk. Exposure of the whole population occurs predominantly through the food chain. Exposure to such chemicals was highest in the 1960s and 1970s. Because of regulation in the 1970s, exposure has declined substantially in the population. The change in incidence of NHL in Sweden and other countries may serve as a good example of how prohibition and limitation of exposure may be reflected in cancer statistics some decades later. **Key words:** incidence, non-Hodgkin lymphoma, persistent organic pollutants, pesticides, prevention. *Environ Health Perspect* 111:1704–1706 (2003). doi:10.1289/ehp.6270 available via <http://dx.doi.org/> [Online 2 July 2003]

Non-Hodgkin lymphoma (NHL) belongs to the types of malignant diseases that have shown the largest increasing incidence in Sweden and in other Western countries during the second half of the 20th century. According to statistics in the National Swedish Cancer Registry, the yearly age-standardized incidence increased significantly for NHL during 1971–1990, an average of 3.2% for men and 3.1% for women (National Board of Health and Welfare 1993). The corresponding figures for 1991–2000 were –0.8% and –0.2%, respectively (National Board of Health and Welfare 2002a). A clear change of the incidence was seen about 1990 (Figure 1).

In the 1990s, the increasing incidence of NHL also leveled off in Denmark (study period 1989–1998; Danish Cancer Registry 2002) and in Finland (study period 1954–2000; Finnish Cancer Registry 2003), but not in Norway (1955–2000; Cancer Registry of Norway 2003) or in the United Kingdom (1971–1997; National Statistics 2001).

The Surveillance, Epidemiology, and End Results (SEER) Program (2003) of the National Cancer Institute is the most authoritative source of information on cancer incidence in the United States. Data have been collected from certain states beginning in 1973; 1999 is currently the last year with available data. The annual percentage change, based on rates that are age adjusted to the 2000 U.S. standard population by 5-year age groups, for all races and both sexes, was +3.6% ($p < 0.05$) during 1973–1990, +1.6% during 1990–1995, and –0.9% during 1995–1999. However, the declining incidence

was seen only in men, although a declining mortality was seen in both sexes during 1990–1995. The increasing incidence of NHL since 1973 clearly leveled off during the 1990s (Ries et al. 2002).

Are there any etiologic agents that can be associated with the changing incidence of NHL in Sweden and other countries? The etiology of NHL is only partly known. Immunosuppression, both acquired and hereditary, has been described to increase the risk, for example, of drug-induced immunosuppression after organ transplantation, infection with human immunodeficiency virus (HIV), and certain autoimmune diseases. Also, viruses, especially Epstein-Barr virus (EBV), have been postulated to be of etiologic significance (Evans and Mueller 1990).

These risk factors cannot explain the observed changes of the incidence of NHL, however. The initial large increase of the incidence and later stabilizing or even decreasing incidence might be explained by one or several environmental agents with decreasing exposure of the population (e.g., because of regulation). Because the tumor-induction period in lymphomagenesis, as for other malignant diseases, varies from years to decades, regulation of such risk factors would probably have occurred during the 1970s and 1980s.

In this article, we discuss results from our studies and those of others since the late 1970s about the association between some chemical compounds and the risk for NHL. Our hypothesis is that changes in exposure to these compounds may at least partly explain the observed changes of NHL incidence, with

Sweden as one example. Our intention is not to give a complete review of the etiology of NHL (for review, see, e.g., Hardell and Axelson 1998; Hardell et al. 2003). Risk estimates and exposure frequencies in our studies enable calculation of the attributable fraction, that is, the proportion of cases that can be attributed to the particular exposure. This was calculated as the exposed case fraction multiplied by $[(OR - 1)/OR]$, where OR is the odds ratio.

Phenoxyacetic Acids and Chlorophenols

Phenoxyacetic acids were synthesized during World War II and were widely and increasingly used as herbicides (including on hardwood trees) from the early 1950s both in Sweden and in other countries. The chemically related chlorophenols were primarily used as impregnating agents.

Our first study on risk factors for NHL in men, which was initiated by a clinical observation (Hardell 1979), was published in 1981. We found a significant association between exposure to phenoxyacetic acids and chlorophenols and malignant lymphoma, both NHL and Hodgkin disease (Hardell et al. 1981). The results for NHL were also published separately (Hardell et al. 1994) and have been replicated by other research groups both in Sweden (Persson et al. 1989) and in other countries (Zahm et al. 1990; for updated review, see Hardell et al. 2003).

Our first investigation on NHL included patients diagnosed during 1974–1978 and mainly assessed exposures from the late 1940s and later (Hardell et al. 1981, 1994). The phenoxyacetic acids 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) constituted Hormoslyr (Gullvik, Sweden), one of the most widely used pesticides in Sweden during that period. 2,4,5-T was contaminated with dioxins during the production. Most hazardous among these dioxins was 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), one of the most toxic chemicals in the world and now classified as a group I human carcinogen

Address correspondence to L. Hardell, Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden. Telephone: 46-19-602-10-00 Fax: 46-19-10-17-68. E-mail: lennart.hardell@orebroll.se

This work was supported by grants from Cancer-och Allergifonden, Nyckelfonden, Örebro Cancer Fund.

The authors declare they have no conflict of interest.

Received 10 February 2003; accepted 1 July 2003.